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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/402,634	03/27/2000	BARBARA RONIKER	CU-2019-RJS	6230

7590 09/26/2005

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EXAMINER	
JAGOE, DONNA A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 09/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/402,634	RONIKER ET AL.	
	Examiner	Art Unit	
	Donna Jagoe	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,15-17,19-24,26-32,34-43,45-52,54-62 and 64-68* is/are pending in the application.

4a) Of the above claim(s) *32 and 34--39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,15-17,19-24,26-31, 40-43, 45-52, 54-62 and 64-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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In view of the remand by the Board of Patent Appeals entered on 18 November 2004, PROSECUTION IS HEREBY REOPENED. A new ground of rejection is set forth below.

Claim(s) 1-12, 14, 18, 25, 33, 44, 53 and 63 have been canceled. Claims 32 and 34-39 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 13, 15-17, 19-24, 26-31, 40-43, 45-52, 54-62 and 64-68 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 24, 40 and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicant has entered claims drawn to a method for prophylactic treatment (claim 13), a method for reducing risk of atherosclerosis (claim 24), a method for reducing risk of an onset of a pre-clinically evident stage of a cardiovascular disorder (claim 40) and a method for reducing risk of an onset of a clinically evident cardiovascular disorder (claim 49), however, applicant has not provided any information in the instant specification regarding how one would reasonably apprise such candidates for treatment. The NCEP (National Cholesterol Education Program)

recommends that treatment decisions be based on the calculated level of LDL (for patients with elevated LDL>=160mg/dl), for those who have fewer than two risk factors in addition to elevated LDL and who do not have clinical evidence of atherosclerotic disease, the goal of treatment is an LDL level <160mg/dl (see Merck Manual, Section 2, chapter 15 Hyperlipidemia topics (W). Applicants' instant specification lacks a written description as to how one would identify the patient population for the treatment of claims 13, 24, 40 and 49, therefore the claims are not enabled. Is the medication to be administered like a vitamin? What age group is targeted?

Claim 13 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of cardiovascular diseases, does not reasonably provide enablement for prophylactic treatment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The term "prophylaxis" is synonymous with the term "prevention" or "curing", and both circumscribe methods of treatment having absolute success. Since absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex/poorly characterized as cardiovascular disease, the specification is viewed as lacking an adequate written description of same.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have

required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1. **The quantity of experimentation necessary**

Applicant fails to provide information allowing the skilled artisan to ascertain which combinations of lipid lowering agents and COX-2 inhibitor agents can reasonably be expected to produce the effect of prophylaxis against the recited cardiovascular diseases, let alone how a patient/candidate would be selected or in which risk factors a patient candidate would have that would result in the recited prophylaxis. The instant claim is very broad and reads on combinations of any COX-2 inhibitors and any lipid-lowering agent, encompassing an overwhelming number of possible combinations, necessitating an exhaustive and undue search for all the embodiments suitable to practice the claimed invention. Given the sheer number of potential combinations, the diversity of potential lipid lowering agents available, and the recognized unpredictability of this art with

regard to uncontrollable risk factors, one would have to mount a massive additional research campaign to determine which combinations within the scope of the instant claims would exhibit the required effect. Accordingly, applicant has failed to provide information sufficient to practice the claimed invention absent resorting to undue experimentation.

2-3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no guidance for selecting any particular patient/candidate for prophylaxis. There is only one working example of an APOe mouse model for atherosclerosis but it is not clear how the mouse is treated and with what agents it is treated.

4-7. The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art:

While the relative skill of those in the art is high, this is outweighed by the highly unpredictable nature of the invention. The prior art recognizes that a long-standing problem exists with regard to absolute success in prophylaxis of cardiovascular diseases. There are several risk factors for heart disease; some are controllable, others are not. Uncontrollable risk factors include: Male sex, older age, family history of heart disease, post-menopausal female, race (Blacks and Mexican Americans are more likely to have heart disease than whites). Still,

there are many risk factors that can be controlled. Controllable risk factors include: Smoking, High LDL, or "bad" cholesterol and low HDL, or "good" cholesterol, Uncontrolled hypertension (high blood pressure), physical inactivity, obesity (more than 20% over one's ideal body weight), uncontrolled diabetes, high C-reactive protein, uncontrolled stress and anger.

Thus, the ability of any given drug combination to prophylax against any given cardiovascular disease cannot be predicted *a priori*, and must be determined empirically on a case-by-case basis. Especially with regard to recited cardiovascular disorders such as viral induced inflammation associated with surgical procedures. What surgical procedures are contemplated in the claims? These are not recited.

8. **The breadth of the claims**

The rejected claims are extremely broad. The term "prophylaxis" is synonymous with the term "prevention" or "curing", and both circumscribe methods of treatment having absolute success. Since absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex as cardiovascular disease, the specification is viewed as lacking an adequate written description of same.

Claim 24 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling treatment, does not reasonably provide enablement

for reducing risk of atherosclerosis in a subject at risk of developing atherosclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

1. **The quantity of experimentation necessary**

Applicant fails to provide information allowing the skilled artisan to ascertain which combinations of lipid lowering agents and COX-2 inhibitor agents can reasonably be expected to produce the effect of reducing risk of atherosclerosis in a subject at risk of developing atherosclerosis, let alone how a patient/candidate would be selected or in which risk factors a patient candidate would have that would result in the recited risk reduction. The instant claim is very broad and reads on combinations of any COX-2 inhibitors and any lipid-lowering agent, encompassing an overwhelming number of possible combinations, necessitating an exhaustive and undue search for all the embodiments suitable to practice the claimed invention. Given the sheer number of potential combinations, the diversity of potential lipid lowering agents available, and the recognized unpredictability of this art with regard to uncontrollable risk factors, one would have to mount a massive additional research campaign to determine which combinations within the scope of the instant claims would exhibit the required effect. Accordingly, applicant has failed to provide information sufficient to practice the claimed invention absent resorting to undue experimentation.

2-3. <u>The amount of direction or guidance provided and the presence or absence of working examples</u>

The specification provides no guidance for selecting any particular patient/candidate for reducing risk of atherosclerosis in a subject at risk of developing atherosclerosis. There is only one working example of an APOe mouse model for atherosclerosis, but it is not clear how the mouse is treated and with what agents it is treated.

4-7. <u>The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art:</u>

While the relative skill of those in the art is high, this is outweighed by the highly unpredictable nature of the invention. The prior art recognizes that a long standing problem exists with regard to absolute success in reducing risk of atherosclerosis in a subject at risk of developing atherosclerosis. There are several risk factors for heart disease; some are controllable, others are not. Uncontrollable risk factors include: male sex, older age, family history of heart disease, post-menopausal female, race (Blacks and Mexican Americans are more likely to have heart disease than whites). But there are many risk factors that can be controlled. Controllable risk factors include: smoking, high LDL, or "bad" cholesterol and low HDL, or "good" cholesterol, uncontrolled hypertension (high blood pressure), physical inactivity, obesity (more than 20% over one's

ideal body weight), uncontrolled diabetes, high C-reactive protein and uncontrolled stress and anger. Thus, the ability of any given drug combination to reduce the risk of atherosclerosis in a subject at risk of developing atherosclerosis cannot be predicted *a priori*, and must be determined empirically on a case-by case basis.

8. **The breadth of the claims**

The rejected claims are extremely broad. The term "reducing risk of atherosclerosis in a subject at risk of developing atherosclerosis" unclear since it is not recited what risk factors would be present. Since absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex as cardiovascular disease, the specification is viewed as lacking an adequate written description of same.

Claim 40 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling treatment, does not reasonably provide enablement for reducing risk of an onset of a pre-clinically evident stage of a cardiovascular disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with this claim.

1. **The quantity of experimentation necessary**

Applicant fails to provide information allowing the skilled artisan to ascertain which combinations of lipid lowering agents and COX-2 inhibitor agents can reasonably be expected to produce the effect of reducing risk of an onset of a pre-clinically evident stage of a cardiovascular disorder, let alone how a patient/candidate would be selected or in which risk factors a patient candidate would have that would result in the recited risk reduction. The instant claim is very broad and reads on combinations of any COX-2 inhibitors and any lipid-lowering agent, encompassing an overwhelming number of possible combinations, necessitating an exhaustive and undue search for all the embodiments suitable to practice the claimed invention. Given the sheer number of potential combinations, the diversity of potential lipid lowering agents available, and the recognized unpredictability of this art with regard to uncontrollable risk factors, one would have to mount a massive additional research campaign to determine which combinations within the scope of the instant claims would exhibit the required effect. Accordingly, applicant has failed to provide information sufficient to practice the claimed invention absent resorting to undue experimentation.

2-3. <u>The amount of direction or guidance provided and the presence or absence of working examples</u>

The specification provides no guidance for selecting any particular patient/candidate for reducing risk of an onset of a pre-clinically evident stage of

a cardiovascular disorder. There is only one working example of an APOe mouse model for atherosclerosis, but it is not clear how the mouse is treated and with what agents it is treated.

4-7. The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art:

While the relative skill of those in the art is high, this is outweighed by the highly unpredictable nature of the invention. The prior art recognizes that a long standing problem exists with regard to absolute success in reducing risk of an onset of a pre-clinically evident stage of a cardiovascular disorder. There are several risk factors for heart disease; some are controllable, others are not. Uncontrollable risk factors include: male sex, older age, family history of heart disease, post-menopausal female, race (Blacks and Mexican Americans are more likely to have heart disease than whites). But there are many risk factors that can be controlled. Controllable risk factors include: smoking, high LDL, or "bad" cholesterol and low HDL, or "good" cholesterol, uncontrolled hypertension (high blood pressure), physical inactivity, obesity (more than 20% over one's ideal body weight), uncontrolled diabetes, high C-reactive protein and uncontrolled stress and anger. Thus, the ability of any given drug combination to reduce the risk of an onset of a pre-clinically evident stage of a cardiovascular disorder cannot be predicted *a priori*, and must be determined empirically on a case-by case basis.

8. **The breadth of the claims**

The rejected claims are extremely broad. The term "reducing risk of an onset of a pre-clinically evident stage of a cardiovascular disorder" unclear since it is not recited what risk factors would be present. Since absolute success is not reasonably possible with most diseases, especially ones having etiologies as complex as cardiovascular disease, the specification is viewed as lacking an adequate written description of same.

Claim 49 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling treatment, does not reasonably provide enablement for reducing risk of an onset of a clinically evident stage of a cardiovascular disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with this claim.

1. **The quantity of experimentation necessary**

Applicant fails to provide information allowing the skilled artisan to ascertain which combinations of lipid lowering agents and COX-2 inhibitor agents can reasonably be expected to produce the effect of reducing risk of an onset of a clinically evident stage of a cardiovascular disorder, let alone how a patient/candidate would be selected or in which risk factors a patient candidate would have that would result in the recited risk reduction. The instant claim is very broad and reads on combinations of any COX-2 inhibitors and any lipid-

lowering agent, encompassing an overwhelming number of possible combinations, necessitating an exhaustive and undue search for all the embodiments suitable to practice the claimed invention. Given the sheer number of potential combinations, the diversity of potential lipid lowering agents available, and the recognized unpredictability of this art with regard to uncontrollable risk factors, one would have to mount a massive additional research campaign to determine which combinations within the scope of the instant claims would exhibit the required effect. Accordingly, applicant has failed to provide information sufficient to practice the claimed invention absent resorting to undue experimentation.

2-3. **The amount of direction or guidance provided and the presence or absence of working examples**

The specification provides no guidance for selecting any particular patient/candidate for reducing risk of an onset of a clinically evident stage of a cardiovascular disorder. There is only one working example of an APOe mouse model for atherosclerosis, but it is not clear how the mouse is treated and with what agents it is treated.

4-7. **The nature of the invention, state of the prior art, relative skill of those in the art, and the predictability of the art:**

While the relative skill of those in the art is high, this is outweighed by the highly

unpredictable nature of the invention. The prior art recognizes that a long standing problem exists with regard to absolute success in reducing risk of an onset of a clinically evident stage of a cardiovascular disorder. There are several risk factors for heart disease; some are controllable, others are not. Uncontrollable risk factors include: male sex, older age, family history of heart disease, post-menopausal female, race (Blacks and Mexican Americans are more likely to have heart disease than whites). But there are many risk factors that can be controlled. Controllable risk factors include: smoking, high LDL, or "bad" cholesterol and low HDL, or "good" cholesterol, uncontrolled hypertension (high blood pressure), physical inactivity, obesity (more than 20% over one's ideal body weight), uncontrolled diabetes, high C-reactive protein and uncontrolled stress and anger. Thus, the ability of any given drug combination to reduce the risk of an onset of a clinically evident stage of a cardiovascular disorder cannot be predicted *a priori*, and must be determined empirically on a case-by case basis.

8. **The breadth of the claims**

The rejected claims are extremely broad. The term "reducing risk of an onset of a clinically evident stage of a cardiovascular disorder" unclear since it is not recited what risk factors would be present. Further, it is not clear to the examiner how one would reduce the risk of a cardiovascular disorder when the cardiovascular disorder is already present (clinically evident?). Since absolute success is not reasonably possible with

most diseases, especially ones having etiologies as complex as cardiovascular disease, the specification is viewed as lacking an adequate written description of same.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 13, 15-17, 19-24, 26-31, 40-43, 45-52, 54-62 and 64-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ridker et al. NEJM (U) and Dellaria et al. U.S. Patent No. 5,776,984 each taken with M. Oliver (V).

The claims are drawn to the following subject matter:

Ridker et al. teach that thrombus formation is the proximate cause of myocardial infarction, but atherosclerosis, the chief underlying cause is a chronic disease that progresses over decades of life. Laboratory and pathologic data support the idea that inflammation has a role in both the initiation and the progression of atherosclerosis and anti-inflammatory agents may have a role in the prevention of cardiovascular disease (page 973, column 2). Further, aspirin reduces the risk of a first myocardial infarction, thus preventing cardiovascular disease (see abstract). In explanation, Ridker et al. teach that the concentration of C-reactive protein predicts the risk of first myocardial infarction and ischemic stroke, C-reactive proteins is a long term marker of risk, even for events occurring six or more years later and this observation suggests that the effects of inflammation are probably mediated through a chronic process. This observation suggests the possibility that other anti-inflammatory agents may have a role in preventing cardiovascular disease. This provides the **motivation** to employ other anti-inflammatory agents such as COX-2 inhibitors to reduce risk of cardiovascular disease.

Dellaria et al. teach PGHS-2 inhibitors (also known as COX-2 inhibitors) (column 1, lines 9-19) useful in treatment of conditions, which are mediated by PGHS-2 activity such as **prevention of cardiovascular diseases** (column 8, lines 10-25). Dosage levels of about 1 to about 50 mg/kg, preferably about 5 to about 20 mg/kg are

administered to a mammalian patient.

It does not teach the instantly claimed dosage range of 0.1-20 mg/kg.

It does not teach the combination with lipid lowering agents for reducing risk of cardiovascular diseases.

As anyone of ordinary skill in the art will appreciate, preferred dosages are merely exemplary and serve as useful guideposts for the physician. The specific safe and effective amount will vary, with such factors as the particular condition being treated, the physical condition of the patient, the duration of treatment, the nature of the concurrent therapy (if any), the specific dosage form to be used, the carrier employed, the solubility of the formula therein and the dosage regimen desired for the composition. Furthermore, it is routine during animal and clinical studies to dramatically vary dosage to obtain data on parameters such as toxicity. For these and other self-evident reasons, it would have been obvious to use dosages of from 0.1 mg/kg to 20 mg/kg of COX-2 inhibitor. Motivation to employ such dosages would come from routine experimentation combined with the knowledge that the Dellaria et al. teach doses of from 1 to 50 mg/kg and preferably 5 to 20 mg/kg.

Oliver teaches that people with mild or moderate increases in plasma cholesterol and additional CHD risk are treated with lipid lowering agents as a result of several studies, such as the West of Scotland trial which showed the benefit from reducing hypercholesterolemia in healthy men at **risk for CVD** with the use of a **statin**, as well as the clofibrate trial (WHO), Cholestyramine trial (Lipid Research Clinics), and gemfibrozil (the Helsinki Heart trial) (see Oliver, page 1378, column 1, last paragraph to column 2

first paragraph, see also page 1379, bibliography). Oliver teaches that *inter alia* statins are employed to reduce the risk of CVS, but it does not teach the addition of a COX-2 inhibitor.

It is generally true that the use of materials in combination each of which is known for the intended purpose is *prima facie* obvious. *In re Crockett and Hulme*, 126 USPQ 186 (CCPA 1960). The prior art clearly teach that both COX-2 inhibitors and lipid lowering, individually, reduce the risk of cardiovascular disease, and it would be natural to suppose that, in combination, they would produce the same effect and would supplement each other. The idea of combining them would flow logically from the teaching of the prior art and therefore that a claim to their joint use is not patentable. *In re Heinrich*, 46 CCPA 933 268 F.2d 753, 122 USPQ 388, and cases there cited. The fact that a first component is in no way related to the second component, but where each has the **same utility**, does not detract from the obviousness of combining them. *In re Linder*, 457 F.2d 506, 507 (CCPA 1972). Moreover, it has not been shown that any new or unexpected result would be produced by the method of combining an anti-inflammatory agent with a lipid-lowering agent. The properties of such agents are well known and it would be apparent that an individuals overall risk of cardiovascular disease would be reduced by administering them separately as taught by the prior art. Oliver teaches that people with mild or moderate increases in plasma cholesterol and additional CHD risk are treated with lipid lowering agents as a result of several studies, such as the West of Scotland trial which showed the **benefit from reducing hypercholesterolemia in healthy men at risk for CHD with the use of a statin**, as

well as the clofibrate trial (WHO), Cholestyramine trial (Lipid Research Clinics), and gemfibrozil (the Helsinki Heart trial) (see Oliver, page 1378, column 1, last paragraph to column 2 first paragraph, see also page 1379, bibliography). Dellaria et al. teach PGHS-2 inhibitors (also known as COX-2 inhibitors) (column 1, lines 9-19) useful in treatment of conditions, which are mediated by PGHS-2 activity such as **prevention of cardiovascular diseases** (column 8, lines 10-25). Dosage levels of about 1 to about 50 mg/kg, preferably about 5 to about 20 mg/kg of the COX-2 inhibiting agent are administered to a mammalian patient. In this case, both the references identify the common problem of reducing the risk of cardiovascular disease and since each reference gives a specific example of a single critical parameter, **preventing cardiovascular disease**, and provides explicit guidance tying that parameter to the agents claimed (**COX-2 anti-inflammatory agents and lipid lowering agents**), it is therefore reasonable to conclude that the strength of correlation between references gives rise to reasonable expectation of success from combining them.

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references.

Accordingly, for the above reasons, the claims are deemed properly rejected and none are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna Jagoe whose telephone number is (571) 272-

0576. The examiner can normally be reached on Monday through Thursday from 9:00 A.M. - 3:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Donna Jagoe
Patent Examiner
Art Unit 1614

09/19/2005

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